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Cognitive impulsivity in animal models: Role of response time and reinforcing rate in delay intolerance with two-choice operant tasks

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ABSTRACT

Impulsivity, a key symptom of ADHD (attention-deficit hyperactivity disorder), is also common in obsessive-compulsive and addictive disorders. There is rising interest in animal models of inhibitory-control impairment. Adolescent rats were tested daily in the intolerance-to-delay (ID) task (session 25 min, timeout 20 s), involving choice between either immediate small amount of food (SS), or larger amount of food after a delay (LL). The mixed 5-HT(1A/7) agonist (8-OH-DPAT, 0 or 0.060 mg/kg i.p.) was administered acutely just before the last three sessions at highest delays. In addition to the classical choice parameter (percent LL preference), the spontaneous waiting (termed response time, RT) occurring between end of a timeout (TO) and next nose-poke was calculated. The pace between consecutive reinforcer deliveries is given by the mean inter-trial interval (mITI, i.e. TO + RT). Hence, the impact of any given delay may be proportional to this pace and be expressed as delay-equivalent odds, i.e. the extent by which delays are multiples of the mITI. Data revealed that RT/mITI increased sharply from around 15 s/35 s to around 30 s/50 s when imposed delay changed from 30 s to 45 s (i.e. odds from 0.91 to 1.06). This suggests that rats adopted a strategy allowing them to keep in pace with perceived reinforcing rate. The increasing delay constraint directly influenced the length of rats' spontaneous waiting (RT) before next decision. For higher delays, with odds >1, rats shifted to a clear-cut SS preference, which is devoid of any exogenous temporal constraint. A challenge with 8-OH-DPAT (0 or 0.060 mg/kg i.p.) decreased impulsive choice but also increased RT. Thus, tapping onto 5-HT(1A/7) receptors slightly enhanced RT/mITI values, possibly reflecting ability of rats to cope with slower reinforcing rates and/or with delay-cancelled reward paces. In summary, delay-induced states of aversion may arise from the innate tendency to rely on a regular rate of reinforcement. Conversely, a drug-enhanced capacity to cope with delay may involve an internal ability to adjust expectancy about such a reinforcing rate.

1. Introduction

Attention-deficit hyperactivity disorder (ADHD) is heterogeneous, highly heritable, and affects 1–2% of children, representing a social burden (Biederman, 1998). Beside core symptoms of hyperactivity and impaired sustained attention, ADHD children often display a disinhibited conduct and impulsivity (Snyder et al., 2002; Willcutt et al., 2005; Doyle, 2006; Castellanos et al., 2006), possibly arising from altered reward processes within fronto-striatal circuits (Sagvolden and Sergeant, 1998; Oades, 1998; Sonuga-Barke, 2005). The deficits in cognitive control and/or motivation, seen in ADHD children, highlight the importance of dopamine (DA) and serotonin (5-HT) systems' disruption in this syndrome (Schultz et al., 1997; Hollander et al., 2000; Casey and Durston, 2006). The variability of ADHD sub-populations, reported in the medical literature, may be partly due to differences in the relative dysfunction between DA and 5-HT systems (Sagvolden and Sergeant, 1998; Oades, 1998).

Altered response-inhibition and impulsivity are key symptoms of ADHD, which have been identified in several other neuropsychiatric conditions (Dell'Osso et al., 2006; Chamberlain and Sahakian, 2007), namely: obsessive-compulsive disorder and other manias (e.g. trichotillo- klepto- and pyro-mania), pathological gambling and other compulsive consummation habits (like addiction e.g. to Internet, to promiscuous sex, to shopping, to substances of abuse). In line with this notion, there has been rising interest for modeling the various facets of impulsivity in laboratory animals (Evenden, 1999). For instance, two-choice operant tasks involve a series of discrete decisions between two reward alternatives, differing for size, nature, operant criteria to meet for obtaining

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them, and/or characteristics of their delivery (Salamone et al., 2007; Roesch et al., 2007; Walton et al., 2007). We have underlined elsewhere (Adriani and Laviola, 2009) that these protocols probe animals for the balance between "innate, sub-cortical" drives and "evolved, cortical" processes. In other words, these tasks allow to evaluate a cognitive ability, i.e. to inhibit sub-cortical drives and to express a more controlled response. Self-control is known to require intact serotonergic function (Wogar et al., 1993; Harrison et al., 1997; Puumala and Sirvio, 1998; Dalley et al., 2002), especially within the pre-frontal cortex (McClure et al., 2004; Ridderinkhof et al., 2004) and its cortico-striatal projections (Cardinal et al., 2004; Christakou et al., 2004).

This kind of two-choice tasks shall be calibrated appropriately (Adriani and Laviola, 2009), so that one alternative leads to "optimal" benefit, i.e. the raw convenience in terms of quantitative foraging (or any other measurable revenue), while the other alternative may provide an "affective" benefit, with a more emotional outcome (i.e. better feeling and/or avoidance of adverse mood). Interestingly, when the optimal benefit loads on one option and affective benefit loads on the other one during the task, experimental subjects may develop a strong sub-optimal preference. This appears however fully justified when based on innate, temperamental attraction for specific features of gratification. For instance, within intolerance-to-delay (ID) tasks (Evenden and Ryan, 1996, 1999), it is assumed that the constraint of waiting for delayed gratification generates aversive states that could subjectively justify the strategy of shifting towards immediate delivery of a smaller-size reinforcer, despite lower payoff in the long term. It has long been known that, as the delay to a reinforcer increases, its reinforcing value decreases (Mazur, 1997). The discounting functions show how rewards' subjective values change as a function of the time necessary to obtain them (Green and Myerson, 2004). Different theories have proposed various equations to describe the relation between delay and reinforcer value (e.g. Hull, 1943; Ainslie, 1975; Gibbon, 1977; Mazur, 1987, 1997; Shull and Spear, 1987; Green et al., 1994). More recently, Ho et al. (1999) have developed the "multiplicative hyperbolic model", which attempts to bring together the several quantitative principles of choice behavior. This model assumes that the subjective value of a positive reinforcer increases as a hyperbolic function of its size, and decreases as a hyperbolic function of its delay and/or the odds against its occurrence. Mazur (1995) demonstrated that the effectiveness of delay-signalling lights in sustaining choice responses is due to its action as a conditioned reinforcer that precedes and predicts the primary reinforcer. The strength of such a conditioned reinforcer is inversely related to the total time (i.e. the delay interval) spent in its presence before the primary reinforcer is delivered. It is quite evident that a refinement of ID tasks can be highly relevant to a deeper validation of new preclinical models of ADHD.

In this respect, however, it is important to underline the notion that impulsive choices may arise in some individuals because of a differential perception of time itself (Wittmann and Paulus, 2008) and/or reinforcing rate during a task (see e.g. Gallistel and Gibbon, 2000; Podlesnik and Shahan, 2008). Indeed, experimental subjects might over- (or under-) estimate the duration of time intervals, and thus experience an enhanced (or a diminished) "psychological cost" associated with the waiting constraint. Alternatively, since experimental subjects quickly adapt to emit responses according to a perceived task reinforcing rate, they may cope with waiting requirement by setting an "acceptable" temporal distance between reinforcing events. There is considerable literature on rat's spontaneous waiting before initiating the next trial. A formal model of voluntary waiting, termed "linear waiting model", has been developed (Staddon et al., 1991; Innis et al., 1993). These authors demonstrated that duration of pauses following food presentation (termed post-reinforcement pauses, PRP) was determined by the preceding inter-food interval. Under simple fixed-interval (or cyclic-interval) reinforcement schedules, the average pause following food presentation stabilizes (or adjusts) at a constant proportion (about one half to two thirds) of the inter-food interval (Schneider, 1969). This adaptive behavior has been termed "temporal tracking", in that the average pause following food presentation tracks the changes in inter-food interval durations (Innis and Staddon, 1971). As such, after each reward delivery and its timeout, the next decision will be expressed after an individually variable period, termed response time (RT), which is however a function of the imposed timeout (TO), since their sum (TO + RT) denote the duration of inter-food intervals. Of course, different subjects may well over- (or under-) estimate their internal setting of such an infradian rhythm, and this could reflect on either a diminished (or enhanced) "subjective cost" of the waiting constraint. In the present paper, we propose and discuss possible influences by this "time (or rate) bias" on decision making within the ID task. We propose that imposed delays are perhaps to be compared to individual, subjective reinforcing rates. Altogether, present results will provide room for theoretic understanding of individual differences, in terms of baseline levels of impulsive (BLI) behavior.

We presently provide a pharmacological validation of the notion of a possible "time (or rate) bias" in the ID task. Indeed, the serotonin (5-hydroxy-tryptamine, 5-HT) receptor type 7 (5-HT(7)) appears to be a good candidate for the setting of an internal, infradian rhythm. It has been indeed proposed that the 5-HT(7) receptor system could be involved in subserving circadian rhythms via the hypothalamic internal clock (Hedlund and Sutcliffe, 2004; Gannon, 2001). An altered perception of time intervals and temporal rates may be postulated in animals treated with 5-HT(7) agonist or antagonist drugs. Our group has recently demonstrated a modulation of baseline impulsivity in rats treated with a 5-HT(7) antagonist (Leo et al., 2009). Indeed, 8-OH-DPAT is a mixed 5-HT (1A/7) agonist, well-known for effective modulation of impulsivity in adult rats (see Poulos et al., 1996; Evenden and Ryan, 1999; Bizot et al., 1999). Such an effect is possibly due to a stimulation of 5-HT (7) receptors, since it was not blocked by the 5-HT(1A) antagonist WAY-100635 (Bizot et al., 1999). Similarly, in reaction-time tasks, 8-OH-DPAT decreases premature responding (Winstanley et al., 2003; Blokland et al., 2005; but see Carli and Samanin, 2000). Other results in operant behavioral tasks confirm that 8-OH-DPAT alters temporal differentiation (Body et al., 2002a,b), and may disrupt timing abilities (Asgari et al., 2006; Chiang et al., 2000). We hypothesized that, since 8-OH-DPAT could affect the internal rate setting of experimental rats, its influence on ID task decision making could possibly tap onto a "time (or rate) bias" rather than onto "true" modulation of a self-control capacity. Altogether, present results provide insights on a key role for 5-HT(1A/7) receptors in delay-based "impulsive" behavior.

2. Methods

2.1. Animal subjects and treatment design

Animal experimental protocols were approved by institutional authorities, on behalf of Ministry of Health, in close agreement with European Community Directives and Italian Law. All efforts were made to minimize animal suffering, to reduce the number of animals used, and to use alternatives to *in vivo* testing.

The experiment used 10 litters of Wistar pregnant female rats (Harlan, Italy), housed in an air-conditioned room (temperature 21 ± 1 °C, relative humidity 60 ± 10%) with a 12-h light/dark cycle (lights on at 8.00 a.m.). Water and food (Enriched Standard Diet, Mucedola, Settimo Milanese, Italy) were available *ad libitum*. On day of delivery, postnatal day (PND) zero, pups were culled to 6 males and 2 females. Only three male siblings per litter were used in the present experiment, housed in pairs of non-siblings, and tested during the adolescent period (PND 30–44) in the intolerance-to-delay (ID) task. After the first four delay sessions, those

rats (ten subjects) demonstrating insensitivity to delay were assigned to the delay-insensitive subgroup and discarded from the drug treatments (Adriani et al., 2003, 2004). The delay-sensitive rats (twenty subjects) were randomly assigned to either challenge with 8-hydroxy-2(di-n-propylamino)tetralin (8-OH-DPAT, Sigma Aldrich, Milan, Italy, at the dose of 0.060 mg/kg) or saline injection for 3 days. Rats underwent ongoing drug treatment with this mixed 5-HT(1A/7) agonist (or vehicle) 30 min before the operant session. This was to assess the ongoing effects of a mixed serotonergic agonist, mainly acting over 5-HT(1A) auto-receptors but also targeting 5-HT(7) (see also Leo et al., 2009).

2.2. Behavioral impulsivity task

Animals underwent a delay intolerance protocol, involving a choice between either a single-pellet, immediate or a fivefold, delayed food reward (see Adriani et al., 2003, 2004; Evenden and Ryan, 1999). The body-weight gain of adolescent rats in free-feeding condition and under food restriction was known from previous experience (Adriani et al., 2003). We planned to reduce rats' daily gain to approximately 2 g/day, i.e. 2/3 off their free-feeding body-weight gain. In order to do this, we removed the tray food 2 days before the experiment started. In order to maintain rats throughout the experiment, in addition to pellets earned during sessions that correspond to a mean of 6.75 g (i.e. approximately a half of a daily meal), extra 8.5 g ± 1.5 g of standard food was given in the home cage after each daily session. Accordingly, rats' weight on the last three testing sessions was 109.35 g ± 1.96 g; 110.75 g ± 1.92 g; 112.05 g ± 2.03 g.

The food restriction was necessary to increase rats' motivation to work for food delivery during the task. However, food restriction level obviously affects choice in delayed-reinforcement paradigms, with more severe restriction having more marked motivation-enhancing effects (Bradshaw et al., 1983; Ho et al., 1999; see also among others: Leander, 1973; Takahashi and Singer, 1980; Papasava et al., 1986; Lamas and Pellón, 1995; Haberny et al., 2004). Each animal was then placed daily in a computer-controlled operant chamber (Coulbourn Instruments, Allentown, PA, USA), provided with two nose-poking holes, a chamber light, a feeder device, a magazine where pellets (45 mg, BioServ, Frenchtown, NJ, USA) were dropped, and a magazine light. The nose-poking in either hole was detected by a photocell and was recorded by a computer, which also controlled food delivery. After the 25-min session, animals were returned to their home cage, and given extra standard chow (approx. 7–10 g/each).

During the training phase (six days), nose-poking in one of the two holes resulted in the delivery of five pellets of food, whereas nose-poking in the other hole resulted in the delivery of one pellet of food. After nose-poking in either hole, and before food delivery, the chamber light was turned on for 1 s. Following food delivery, the magazine light was turned on for 20 s, during which nose-poking was recorded but was without scheduled consequences (timeout). During the testing phase (eight days), a delay was inserted between nose-poking and large-reward delivery. The chamber light was kept on to signal the entire length of this delay. The small reward delivery was unchanged. Hence, animals had choice between a "LARGE & LATE" (LL) or a "SMALL & SOON" (SS) reward. The delay length was kept fixed for each daily session, and was changed progressively over days (from 0 s to 7 s, 15 s, 30 s, 45 s, 60 s, 75 s and finally 90 s on the eighth day). Animals received the drug challenge(s) at the three longest delays of this sequence.

2.3. Design and data analysis

Data were analyzed by split-plot ANOVA. The general design of the experiment had a 2-level drug factor (denoting acute challenge with the agonist drug *vs* vehicle) × delay (set for each session). The litter was always the blocking unit, and the ANOVA design comprised all within-litter factors. This approach is often used and even recommended in studies involving developmental treatments (Zorrilla, 1997). Multiple comparisons were performed with Tukey HSD. Criterion for exclusion was LL preference lower than 50% at the end of the training phase, but it was not necessary to exclude any rat from data analyses on the basis of this criterion. Assignment to the delay-insensitive subgroup ("flat", see Adriani et al., 2003) was made when LL preference at delay = 45 s was higher than that shown at delay = 0 s. Ten rats were found to satisfy such criterion.

In the present paper, an innovative dependent variable termed response time (RT) was calculated, according to the general procedure described elsewhere (e.g. Adriani and Laviola, 2006, 2009). Briefly, the total time of a session (25 min = 1500 s) was divided into two components, defined as T(wasted) and T(deciding). One portion of session time can be considered as "wasted" because of post-delivery timeout periods, during which no effective demanding is possible. Then, the remaining portion of session time is entirely available to rats for making a decision about the next "adequate" nose-poke. The response time (RT), denoting the average spontaneous waiting before each nose-poke, and hence the mean inter-trial interval (mITI), can be calculated as described in Table 1. Then, curves for average spontaneous waiting (RT) were created for present animals, with the values of response time on *Y*-axis plotted against raw delay duration on *X*-axis (see Fig. 1).

The ID task testing phase consisted indeed of two halves: 1) first four sessions, when delays (up to 30 s) were introduced but animals were allowed to face them in drug-free conditions; and 2) last four sessions at the highest delays (45 s and more), including a baseline reference point plus the last three sessions, when the acute challenge was also administered. Separate analyses were performed within these two testing-phase halves. Preliminary ANOVAs were conducted on the first half, to ascertain that rats assigned to SAL injection did not differ from their siblings assigned to the drug challenge. Then, ANOVAs to evaluate the ongoing drug's effects were indeed conducted on results from the second half (Leo et al., 2009).

Table 1
Formulas used for calculations on data from the present experiment.

T(wasted) = (no. of SS rewards) × (timeout) + (no. of LL rewards) × (delay + timeout)
T(deciding) = (total session time) − T(wasted)
spontaneous waiting (RT) = T(deciding)/(total no. of SS + LL rewards)
mean Inter-Trial Interval (mITI) = timeout (TO) + spontaneous waiting (RT)
Odds = delay/mITI *or* Delay = mITI × odds

The second dependent variable considered was the "classical" choice (%) for the large reinforcer, namely percentage of LL over total LL + SS choices, during the test phase (Evenden, 1999). To get a precious index of the impact exerted by the delay, we proposed to look at delays in terms of "odds against discounting" (Adriani and Laviola, 2006, 2009). For the ID protocol, delay-equivalent odds value can be estimated as a proportion of the mITI, indicative of all SS events which are lost to the subject because of the LL-bound delay. In other words, the delay-equivalent odds value represents the number of crucial mITI intervals, i.e. the sum of all the timeout (TO) periods plus all average spontaneous-waiting periods (RT), which would have been generated by all the "lost" SS opportunities, and that could well fit within the whole time constraint elapsed for any LL event (see Adriani and Laviola, 2006, 2009). This delay-equivalent odds value is an interesting index that tells us about the magnitude of the delay compared to the reinforcing rate of the task, which is paced by the crucial mITI interval. We calculated, at each imposed delay value, the mITI really expressed by animals and hence the delay-equivalent odds value. We used the formulas reported in Table 1 and results are reported in Table 2. The typical ID task curves for present animals were thus generated, but percent LL preference on *Y*-axis were plotted against delay-equivalent odds, instead of raw delay duration, on *X*-axis (see Fig. 2).

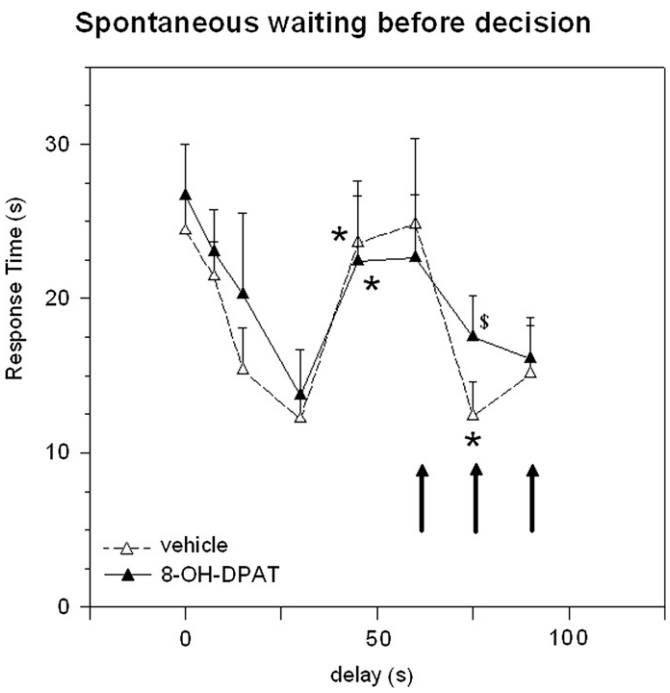

Fig. 1. Mean (±SEM) response time (RT), i.e. the spontaneous waiting between the end of a timeout period and the following nose-poke for a reinforcer (either LL or SS), shown by adolescent rats in the ID task. The 8-OH-DPAT (0 or 0.060 mg/kg i.p.) was administered acutely, 30 min before the last three sessions at highest delays (see arrows). In the 8-OH-DPAT group, time needed to express a decision was somewhat prolonged. *$p < 0.05$ when comparing each point to the preceding one. \$$p < 0.05$ when comparing vehicle- and drug-injected animals ($n = 10$ each).

Table 2
At each imposed delay value, the mITI really expressed by animals and the delay-equivalent odds value were calculated, using the formulas reported in Table 1. The crucial mITI intervals derive directly from the average spontaneous-waiting periods (RT, see Fig. 1 and Table 3) plus the fixed timeout period (TO, 20 s in this experiment) of all rats, irrespective of individual delay-sensitivity. The delay-equivalent odds values were then used as *X*-axis values for Fig. 2. Values are given as means ± SEM ($n = 30$).

Delay (s)	mITI	Delay/mITI = odds
0	49.58 ± 7.12	0
7	43.08 ± 2.39	0.17 ± 0.01
15	36.92 ± 2.13	0.43 ± 0.02
30	34.51 ± 1.70	0.91 ± 0.03
45	52.32 ± 7.87	1.06 ± 0.07
60	44.62 ± 3.33	1.53 ± 0.07
75	40.82 ± 5.00	2.15 ± 0.08
90	41.10 ± 3.70	2.55 ± 0.13

3. Results

3.1. Response time

The general ANOVA, considering the whole testing phase, yielded a main effect of delay, $F(7,126) = 5.29$, $p < 0.001$, supporting a non-linear, sigmoid shape of the curve. Specifically, a marked discontinuity was evident between imposed delays of 30 s and 45 s (i.e. odds of 0.91 and 1.06). This peculiarity was somewhat unexpected, since the rats' preference was indeed similar for both delays (around indifference, see below). The finding of such peculiarity provided an evidence-based justification allowing to split the whole ID task testing phase into two halves, as described in the Methods section. Separate analyses were thus conducted.

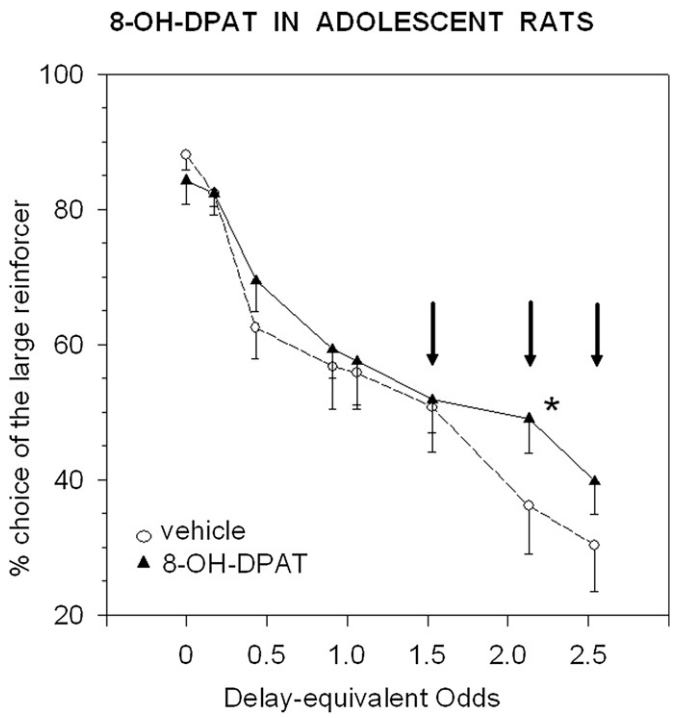

Fig. 2. Effect of the 8-OH-DPAT, a mixed 5-HT(1A/7) agonist, on impulsivity shown by adolescent rats in the ID task. Mean (±SEM) demands (%) for the large reinforcer (LL) on *Y*-axis are plotted against delay-equivalent odds, instead of raw delay duration, on *X*-axis. At each imposed delay value, the delay-equivalent odds value was calculated using the mITI really expressed by animals (i.e. the average spontaneous-waiting periods, RT, see Fig. 1, plus the fixed timeout, TO, period of 20 s in this experiment). These values, calculated using the formulas in Table 1, are reported in Table 2. Arrows denote injection with 8-OH-DPAT (0 or 0.060 mg/kg i.p.), which was able to significantly enhance the LL preference at delay = 75 s. *$p < 0.05$ when comparing vehicle- and drug-injected animals ($n = 10$ each).

The first half ANOVA yielded a main effect of delay, $F(3,54) = 10.4$, $p < 0.001$, confirming a progressive reduction of response time when moving from no delay to a 30 s delay. In other words, after the end of a timeout, decisions to nose-poke were made progressively more quickly. The average spontaneous waiting (RT) time decreased from around 30 s down to around 15 s (similarly to what found previously for adolescent rats, see Adriani and Laviola, 2006). As expected, no difference emerged between control and to-be-challenged rats.

The second half ANOVA yielded a main effect of delay, $F(3,54) = 6.99$, $p < 0.001$, again confirming a progressive reduction of response time when moving from 45 s to 90 s delay. There was also a drug by delay interaction, $F(3,54) = 1.83$, $0.10 < p < 0.05$, indicating an effect of mixed 5-HT(1A/7) stimulation. Post hoc analyses revealed that a significant difference between control and drug-challenged rats only emerged with a 75-s delay. Indeed, the RT was again very quick in control animals. In the group treated with 8-OH-DPAT, however, RT values decrease less sharply, suggesting prolonged time span before expressing nose-poking. This picture is possibly consistent with decreased impulsive choice, observed with mixed 5-HT(1A/7) stimulation (see below).

3.2. LL preference as a function of delay-equivalent odds

LL preference of adolescent rats displayed a progressive decrease across sessions, delay $F(3,54) = 22.9$, $p < 0.001$, but still remained above the level of indifference. Then, rats were challenged with the mixed 5-HT(1A/7) agonist 8-OH-DPAT (or vehicle) on the second half of testing phase, when LL choices were progressively decreasing across the level of indifference (50%) and towards a clear-cut SS preference, delay, $F(3,54) = 8.83$, $p < 0.001$. Interestingly, LL choices were significantly higher in drug-injected rats than in the corresponding controls, drug × delay interaction, $F(3,54) = 3.83$, $p < 0.05$ (see Fig. 2). Specifically, post hoc analyses revealed significant difference between drug- and SAL-challenged rats upon the second injection at the 75 s delay, i.e. at odds = 2.15. As outlined above, increased LL preference comes along with higher RT values, perhaps suggesting an attempt to adapt on a slightly prolonged reinforcing pace. This picture demonstrates the capacity of a mixed 5-HT(1A/7) agonist to reduce impulsivity. Consistently, waiting ability before next choice also appeared to be increased, although not explicitly required by the task. These findings are observed with 8-OH-DPAT when baseline levels of impulsive (BLI) behavior are enhanced, as is typical of the adolescent phase (Laviola et al., 2003). A very similar picture also characterizes adult rats after 5-HT(7) blockade (Leo et al., 2009).

3.3. Response time and LL preference in the "flat" subgroup

As expected from previous studies (Adriani et al., 2003, 2004), some rats showed no sign of sensitivity or reactivity to the increasing delay, and continued to prefer the LL option all along the task. A slight decrease towards indifference was evident at the two highest delays, but a clear-cut SS preference was never exhibited (see Table 3). A formal analysis to compare this subgroup with the two other rat groups was unnecessary, since these subjects were indeed chosen explicitly for such kind of profile. In contrast, it was interesting to explore whether this subgroup would show any change in RT parameter as a function of delay.

The general ANOVA, considering the whole testing phase, yielded no main effect of delay, $F(7,63) = 1.14$, ns, supporting a linear shape of the curve. Separate analyses were also conducted, but neither first nor second half ANOVA yielded any effect of delay,

Table 3
Delay-insensitive adolescent rats in the ID task. Mean response time (RT), i.e. spontaneous waiting (s) between the end of a timeout period and the following demand for a reinforcer (either LL or SS); mean nose-pokes (%) for the large reinforcer (LL). Criterion for assignment to this "flat" subgroup (Adriani et al., 2003) was LL preference at delay = 45 s higher than that shown at delay = 0 s (ten rats). $^{*}p < 0.05$ when comparing to the previous and/or the following points. Values are given as means ± SEM ($n = 10$).

Delay (s)	Response time (s)	LL preference (%)
0	21.18 ± 2.62	66.83 ± 5.45
7	23.88 ± 6.39	67.96 ± 4.22
15	18.41 ± 2.38	66.71 ± 5.07
30	17.60 ± 3.89	65.51 ± 5.04
45	27.05 ± 4.52*	67.81 ± 5.40
60	18.36 ± 3.49	56.65 ± 6.36
75	18.60 ± 2.99	49.22 ± 7.08
90	22.56 ± 6.37	49.21 ± 6.63

$F(3,27) = 1.39$ and 1.32, ns, respectively, confirming no changes of response time when moving across delays. However, post hoc analyses revealed that RT at delay = 45 s was significantly higher compared to the previous and the following points. Similarly to the other two rat groups, a slight discontinuity was also evident for delay-insensitive subjects at imposed delay of 45 s (see Table 3). This peculiarity may be used to suggest that this subgroup of animals was somewhat "sensitive" to delay progression, and the fact that they display little or no change in LL preference may indeed represent lack of "reactivity". Again, the finding of such peculiarity further provides an evidence-based justification, allowing to split the whole ID task testing phase into two halves, as described in the Methods section.

4. Discussion

Most of reports (if not all of them) on two-choice ID tasks exploit the choice of large reinforcement (LL%: percentage of LL over total LL + SS choices) as the principal (if not the only) index for the measurement of cognitive impulsivity (Evenden and Ryan, 1996, 1999). We present novel evidence in favor of a role played by other parameters, like: (1) average spontaneous waiting before a choice is made (response time, RT) and consequently (2) time elapsing between two consecutive reinforcing events (mean inter-trial interval, mITI). The mere value of the delay duration has no universal significance, rather its impact could be dependent on other subjective temporal features within the task. Hence, we propose a new way to look at the subjective impact of a given delay on tested subjects. Specifically, individual coping might impose a given pace to behavioral responses and (mal)adaptation to response-outcome synchrony may explain (sub)optimal reactions. In this line, we assume that the experimental subjects may set an internal, infradian rhythm to cope with the ID task, and hence that the impact of a given delay might be more appropriately compared with this rhythm. In fact, values of such parameters like RT and mITI vary considerably across individuals and also, as we report here, as a function of the fixed, experimenter-imposed delay. We reported earlier about RT and its role in the two-choice ID task (Adriani and Laviola, 2006), and we presently provide a more detailed insight onto the profile of this parameter during the course of the whole ID task, i.e. as a function of delay duration.

A major constraint introduced by the experimenter onto the ID task is the timeout (TO) interval, in that subjects are forced to respond after at least the TO is elapsed. Subjects will spontaneously show a slight interval of further waiting, termed RT. Of course, RT is not only due to decision-making processes, but also (and mainly) because of other non-controlled processes and sources of distraction. However, two consecutive reinforcers will always be spaced by a mean inter-trial interval, i.e. the timeout interval plus the average spontaneous waiting of subjects (mITI = TO + RT). It is known that lab animals are quickly paced to the reinforcing rate of a given task (see e.g. Gallistel and Gibbon, 2000; Podlesnik and Shahan, 2008). When food deliveries occur at regular intervals or at fixed times following a signal, animals' prediction must involve some kind of timing process (Staddon and Cerutti, 2003; Ludvig and Staddon, 2004). A number of theories have been suggested to account for such timing behavior (see, e.g. Gibbon, 1977; Killeen and Fetterman, 1988; Staddon and Higa, 1991; Staddon et al., 1991; Meck and Benson, 2002). A recent study of Lewis et al. (2003) clearly demonstrated that circadian rhythm and interval timing (measurement of learnt short intervals) are two completely independent mechanisms. In the ID task, the overall reinforcing rate is crucially imposed by individual mITI, and the impact of a delay may depend on the extent by which this pacing is altered (see Adriani and Laviola, 2009). The introduction of delay is classically expected to generate states of aversion, but their magnitude may depend on the extent by which the subjective reinforcing rate is disturbed. In other words, we propose that the impact of a given delay is proportional to the subjective adaptation to reinforcing rates, and hence can be expressed as a multiple of the mITI. If the delay is small relative to the crucial mITI value, then the internal rhythm driving overall perception of task reinforcing rate may well be undisturbed. Only delays that are long enough, compared to the crucial mITI value, will considerably generate asynchrony between the subjective rhythmic expectation and actual task reinforcement, thus generating a drive to shift towards SS. As a consequence, a given delay length (e.g. 30 s) might have a quite low impact (i.e. a low odds value) if subjects are paced to very long mITI (e.g. Koot et al., 2009), while it would be perceived as much more frustrating (i.e. equivalent to higher odds values) if subjects are paced to quite a shorter mITI, as in the present study.

The concept of delay-equivalent odds value was first introduced to compare the ID with the probabilistic-delivery (PD) tasks (Adriani and Laviola, 2006). For the ID protocol, delay-equivalent odds value is the number of all SS events, including all their timeout (TO) periods plus an average value for spontaneous waiting (RT, between the end of timeout and the next nose-poke), which could fit within the time constraint (i.e. delay) elapsed for any LL event. The formulas are:

$$\text{mITI} = \text{timeout(TO)} + \text{spontaneous waiting(RT)}$$
$$\text{Odds} = \text{delay}/\text{mITI} \quad (1)$$

As such, the mITI represents a "crucial interval" within the task (Koot et al., 2009; Adriani and Laviola, 2006, 2009). For instance, if we assume that animals have a spontaneous waiting (RT) as low as 15 s in average, within a protocol where the timeout is set at 20 s, then the mITI can be as low as 35 s (see indeed Table 2). In these conditions, a delay = 35 s in the ID task will be equivalent to odds = 1 in a PD task. In fact, a fixed delay of 35 s, triggered by any LL nose-poking, will impose an extra temporal distance of 35 s before the LL delivery, which is by definition followed by 35 s (TO + RT) before the next nose-poking is expressed. Out of these two crucial mITI intervals, the first one is indeed a "lost" foraging opportunity, and this justifies the assumption that odds against discounting is indeed 1 in these conditions. Interestingly, had the subject chosen twice for SS, the same two crucial mITI intervals would elapse, reinforcer delivery would be regularly paced, but the subject would have received two SS pellets instead of five LL altogether. It is now pertinent to discuss whether animals are responsive to this differential long-term payoff and/or the shift from LL to SS is generated because of the altered delivery pace.

The present profile of RT and mITI values suggests that the reinforcer delivery pace is somewhat independent from delay, at least until imposed delays are low. Indeed, the RT and mITI decrease when the imposed delay rises to 7 s, 15 s and 30 s. This profile indicates that animals react to the first, lower delays with a tendency to respond more quickly. We suggest that rats are just trying to preserve the overall reinforcing rate. Indeed, any portion of time elapsed because of imposed delays is reflected by a nearly equivalent narrowing of the spontaneous waiting (RT), as predicted according to a linear waiting model (Innis and Staddon, 1971; see also Innis et al., 1993; Ludvig and Staddon, 2004; Staddon and Cerutti, 2003). However, when delay lengths are further increased (i.e. at delays of 30 s and 45 s), two phenomena come along depicting a turning point in the performance of experimental subjects: 1) animals now express their subjective "indifference point" (i.e. 50% LL and 50% SS choices), which may well be seen as an intermediate step during their shift from the previous LL to a novel SS preference; and 2) the RT suddenly rises and peaks (see Fig. 1) from around 15 s up to around 30 s, giving a corresponding rise in the crucial mITI intervals from around 35 s up to around 50 s.

Thus, the adding of 15 s to the imposed delay results in a 15 s longer RT, a finding that may seem counter-intuitive at first glance. Why a longer constraint of "imposed" waiting should come along with longer "spontaneous" waiting? One way to interpret these findings is that rats are somewhat paced by the imposed delay, which would be incorporated within their internal task-coping rhythm. Consequently, they might express this pacing under the form of "unnecessary" procrastination of their next response (see e.g. Gallistel and Gibbon, 2000; Podlesnik and Shahan, 2008), as if rats were trying to adapt to a time-structure perceived from the task contingencies. Noteworthy, a specific step of the delay progression (i.e. the 30 s and 45 s one) appears to be likely incorporated within the internal-clock rhythm. The consequence is that a similar 15-s rise (i.e. the 35 s and 50 s mITI peak) is also observed in the amount of time elapsing between food delivery and the expression of a next nose-poke, even though the operant system would be fully available to rats after a signaled timeout of 20 s only.

As a further evidence of pace-keeping by rats, calculations (see Table 2) reveal that these two key delay lengths of 30 s and 45 s appear quite similar from a subjective viewpoint, as delay-equivalent odds display just a 0.91–1.06 increase! It is important to underline that rats express indifference for either SS or LL at these delay intervals. Indeed, SS options can lead rats to gain a one-pellet delivery per each crucial mITI interval, while LL options result in the "loss" of one potential mITI-paced food delivery, caused by the delay constraint. Intriguingly, rats' indifference implies that two one-pellet mITI-paced food deliveries (deriving from SS choice) are subjectively perceived as equivalent to the "loss" of one entire mITI-paced delivery plus a five-pellet delivery at the second mITI pace (deriving from LL choice). Hence, despite the objective convenience of LL in terms of overall payoff, these "lost paces" can affect the rats' performance much more than relative sizes of the two alternatives, indeed, as the value of the fivefold, "bulk" prize appears greatly discounted. This situation of subjective indifference is depicted in Fig. 3.

Interestingly, SAL-injected control rats overtly displayed a shift towards SS preference when imposed delays were equivalent to much more than odds = 1 in terms of mITI. This profile suggests that rats may become very intolerant to situations in which the "bulk" prize requires them to invest more than one mITI-paced feeding opportunity. This consideration is confirmed by the striking drop in the RT (back from 30 s to 15 s) observed at delay = 75 s, when control rats ceased to show indifference and overtly exhibited a preference for SS choices. In other words, once the novel SS-preference strategy is established, a drop in the internal rhythm

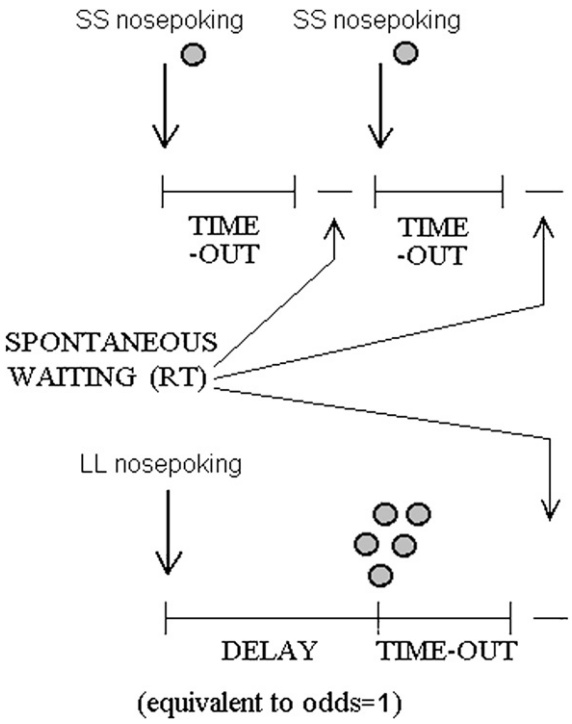

Fig. 3. Schematic comparison between temporal features of SS *vs* LL reinforcement at odds = 1, when rats expressed subjective indifference. Arrows represent nose-poking by rats tested under the ID protocol. In case of SS selection, consecutive trials (nose-poking plus the one-pellet food deliveries) are separated by the timeout (TO, 20 s) plus the spontaneous waiting (response time, RT). In case of LL selection, an odds against discounting of one "lost" feeding pace (before each five-pellet food delivery) is produced when the delay interval is set to be as long as this mean inter-trial interval (mITI). When imposed delay changed from 30 s to 45 s, the RT/mITI increased sharply from around 15 s/35 s to around 30 s/50 s (see Fig. 1), hence the odds remained around one (from 0.91 to 1.06, respectively). Despite their subjective indifference, performance of rats is sub-optimal (each SS selection leads to much lower payoff in term of feeding).

or pace is likely to come along with adaptation to the new reinforcing rate, where the mITI stabilizes around a value as low as 40 s. Indeed, accepting the "loss" of two or more mITI-paced deliveries of food should be necessary to get the "bulk" prize at the longest delays (see Table 1). In these conditions, a quick nose-poking for SS begins to be expressed shortly after a timeout completion, in a quasi-automatic manner, as is confirmed by the low value observed for the RT parameter.

The effect of 8-OH-DPAT consisted of a slight but significant rise in LL selection, and is classically discussed as a lower delay intolerance (Evenden and Ryan, 1996, 1999). The effect was clear at delay = 75 s when, as outlined above, mITI is around 40 s and delay is roughly equivalent to odds = 2. These values imply that, upon drug challenge, rats are apparently more prone to accept (or less disturbed by) the "loss" of a couple mITI-paced feeding opportunities, associated with each LL selection, and this allows them to get the five pellets altogether. While it is clear that, meanwhile, control subjects rather prefer to get three mITI-paced pellets with three consecutive SS selections, 8-OH-DPAT challenged animals are able to select the "bulk-prize" option more often. Noteworthy, the drug effect is evident not only from the LL preference, but also from the RT profile, in that both curves are slightly higher in 8-OH-DPAT than control rats. This finding may indicate either a slower time perception or, perhaps, an adaptive attempt to stay in pace with the increasing delay length, possibly by setting a somewhat longer internal rhythm.

Along with explanations tapping onto temporal mechanisms, another possibility more linked to motivational aspects can be

offered. Specifically, 8-OH-DPAT challenged rats could get a much greater gratification from a fivefold reinforcer. This possibility would rely on attractiveness of a "bulk" size rather than on temporal contingencies like the "loss" of mITI paces. The question of amount-dependent temporal discounting has been extensively investigated in both humans and animals (Farrar et al., 2003; Green et al., 2004; Ong and White, 2004). As a matter of fact, in all previous experiments where reinforcer delay and magnitude have been manipulated, amount-dependent temporal discounting has never been demonstrated (Rodriguez and Logue, 1988; Belke et al., 1989; Ito and Nakamura, 1998; Mazur, 2000). In our opinion, therefore, such alternative could only be verified or ruled out by running a PD task, directly assessing the animals' temptation to gamble (Adriani and Laviola, 2006, 2009).

5. Conclusion

We have recently hypothesized that a functional link might exist between accumbal 5-HT(7) expression and self-control ability in the ID task (Leo et al., 2009). Specifically, a selective 5-HT(7) antagonist was able to enhance basal delay intolerance, and to block the enduring reduction in impulsivity generated from an adolescent exposure to methylphenidate (Adriani et al., 2007). Accordingly, pharmacological modulation of 5-HT(7) system may be useful to control impulsive-behavior symptoms. The present results highlight the need to verify whether that putative role could be ascribed to drug efficacy on temporal mechanisms, such as time perception or infradian rhythm setting, or to an action over more "motivational" processes, such as the subjective attractiveness *vs* discounting of reward. Future studies should actually comprise both these endpoints.

The present results, suggesting delay intolerance to be elicited when delay is equivalent to odds>1, confirm our previous reports (e.g. Koot et al., 2009). In summary, even though a further and deeper validation should be carried out, we propose that the concept of delay-equivalent odds values may allow to compare ID task results across various studies, differing for objective (e.g. the TO, the total session duration, etc.) and for subjective (e.g. the spontaneous RT, and hence the mITI) parameters. Consistently, we propose that food-restricted rodents may experience a delay-induced aversion as a consequence of inability to adapt internal rhythms to changes in the pace of tasks' reinforcing events, sometimes independently from the actual size(s) of food delivery.

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